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Studies toward the total synthesis of cyclodidemniserinol trisulfate. Part I: 3,5,7-Trisubstituted 6,8-dioxabicyclo [3.2.1] octane core structure construction via a convergent and a linear stereoselective synthesis

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ABSTRACT

The core structure of the natural product cyclodidemniserinol trisulfate, a natural HIV-1 integrase inhibitor, was synthesized by employing intramolecular ketal formation strategy via a convergent synthesis and a linear synthesis approach, respectively. Both approaches relied on Shapless asymmetric dihydroxylation to introduce the chiral centers at 1- and 7-position, and the latter also utilized Sharpless asymmetric epoxidation to install the chiral center at 3-postion of the 3,5,7-trisubstituted-6,8-dioxabicyclo [3.2.1] octane. The established methodologies will be beneficial for further total synthesis and structural derivatization.

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Cyclodidemniserinol trisulfate (Fig. 1) was isolated and characterized from extracts of marine invertebrates, the Palauan ascidian *Didemnum guttatum* by Faulkner and co-workers in 2000.[1] This natural marine product is structurally most closely related to didemniserinolipid A from an Indonesian *Didemnum* sp.[2] However, the most notable difference is the presence of a 22-memberd additional ring containing a glycine unit and the presence of sulfate groups. Moreover, cyclodidemniserinol trisulfate not only exhibits cytotoxicity activity, but also inhibits the HIV-1 integrase with an IC_{50} of 60 μg/mL. Although the activity is not high, the new structure as natural HIV-1 integrase inhibitor stimulated our interest to synthesize it. On one hand, although ^{1}H NMR, ^{13}C NMR, COSY, HMBC, HSQC–TOCSY, and MS were utilized to elucidate the structure, the absolute configuration of cyclodidemniserinol trisulfate has not been determined and reported yet. Total synthesis of the compound in a stereoselective manner can help the determination of the absolute configuration. On the other hand, the low content of the cyclodidemniserinol trisulfate in nature restricted its further biological study. Furthermore, the total synthesis can afford general methodology to derivatize the active structure. Natural product-based combinatorial library is an efficient approach for the innovative drug discovery.[3] So, we initiated the project of total synthesis of the natural HIV-1 integrase inhibitor, cyclodidemniserinol trisulfate.

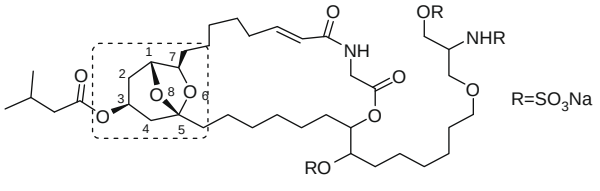

Figure 1. The structure of cyclodidemniserinol trisulfate. The dashed circle indicated the core structure of 3,5,7-trisubstituted-6,8-dioxabicyclo[3.2.1] octane.

By retrosynthetic analysis of the target molecule, we were intrigued to start from synthesizing the 3,5,7-trisubstituted 6,8-dioxabicyclo [3.2.1] octane. This bicyclic ketal-containing structure is widely found in many natural products such as brevicomin,[4] didemniserinolipid B, frontalin,[5] multistriatin,[6] attenol,[7] and pinnatoxin A,[8] some of which display excellent cytotoxicity. Therefore, the 6,8-dioxabicyclo [3.2.1] octane-based combinatorial library afforded promising potent antitumor hits.[9] Since it is the core structure and possesses potential bioactivity, we decided to construct the 3,5,7-trisubstituted-6,8-dioxabicyclo [3.2.1] octane as the first stage of the total synthesis study.

Although many synthetic routes toward 6,8-dioxabicyclo [3.2.1] octane and its derivatives have been reported, only a few involved the 3,5,7-trisubstituted structure. The non-3-substituted analogs can be conveniently synthesized through intramolecular ketal formation reaction between a carbonyl group and a diol group,[7] or Diels–Alder reaction followed by intramolecular radical addition.[10] However, for the 3-substituted structure, few synthesis was reported, employing a different strategy to build the 6,8-dioxabicyclo [3.2.1] octane, in which the ketal moiety was constructed before

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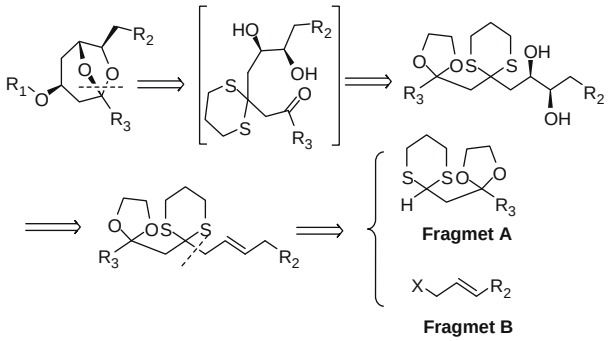
the dioxabicyclic system was formed via an intramolecular alkylation.[11] The main drawback of this approach was the restriction of the 3-substituent structure type and lack of functionality tolerance.

In the context of the total synthesis and structural derivatization, the intramolecular ketal formation strategy would be optimal for the synthesis of 3-substituted 6,8-dioxabicyclo [3.2.1] octane in terms of the functional group tolerance and structural diversity. Herein we thoroughly studied the general approach to synthesize 3,5,7-trisubstituted-6,8-dioxabicyclo [3.2.1] octane by employing intramolecular ketal formation strategy. Two stereoselective synthetic routes were developed, one via convergent synthesis, the other via linear synthesis, to lead to the target molecule successfully.

Strategy one: convergent stereoselective synthesis

On the basis of the retrosynthetic analysis of the bicyclic ketal structure (Scheme 1), the convergent strategy was first chosen. The ketal structure can be transformed into a ketone group and a 1,2-diol group, while the 1,2-diol structure can be transformed into an (*E*)-alkene group. So the target structure was disconnected into two fragments: a thioacetal containing fragment A, and an allylic halide containing fragment B. The thioacetal group can achieve the polar inversion of carbonyl group thus secure the alkylation. In this strategy, the chiral centers could be introduced via Sharpless asymmetric dihydroxylation reaction.[12]

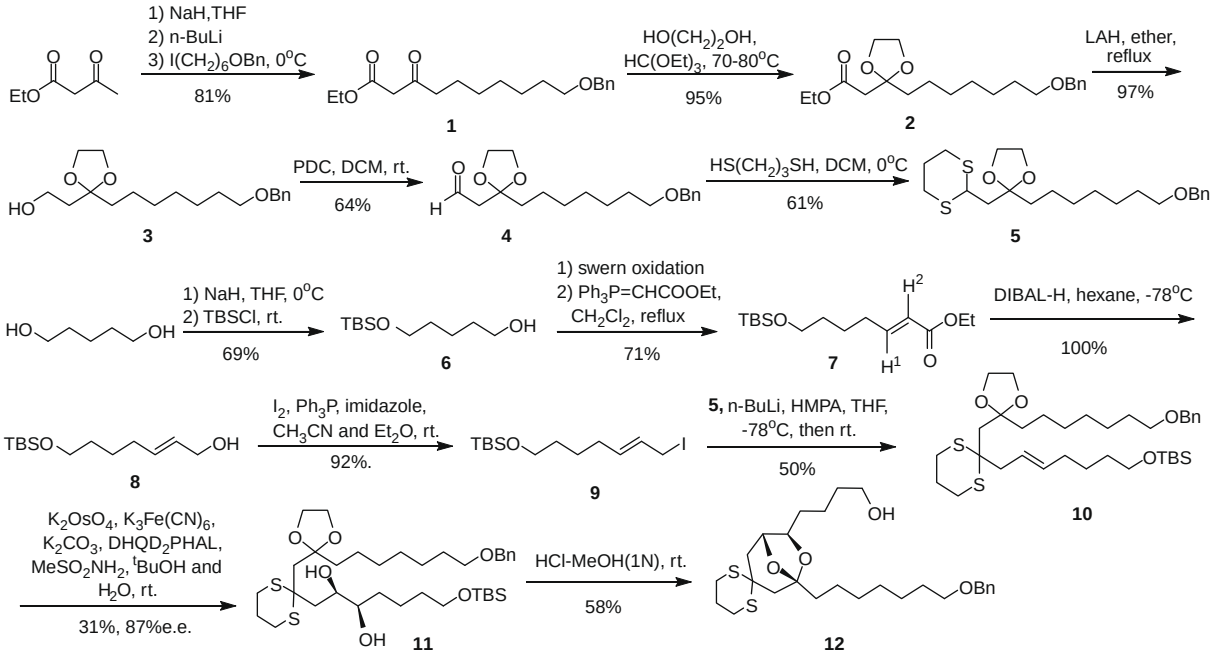


Scheme 1. The retrosynthetic analysis of the 3,5,7-trisubstituted-6,8-dioxabicyclo [3.2.1] octane with strategy one.

The synthetic approach is depicted in Scheme 2. Beginning with the alkylation of the dianion of ethyl acetoacetate[13], the alkyl chain attached acetoacetate **1** was produced in high yield. After the ketone group was protected with ethane-1,2-diol, the ester group was reduced to the alcohol with lithiumaluminium hydride. Oxidation of the primary alcohol **3** with pyridinium dichromate followed by protecting the resultant aldehyde with 1,3-propandithiol furnished the fragment A, thioacetal **5**.

In the synthesis of fragment B, 1,5-pentandiol was used as the starting material. The 1,5-pentandiol was mono-protected by *tert*-butyldimethylchlorosilane (TBSCl), then the resulting alcohol **6** was oxidized via Swern Oxidation followed by condensation with ylide reagent, ethyl phosphoranylidene acetate to give the α,β-unsaturated ester **7**. The coupling constant (*J*) between H^1 and H^2 in the ^1H NMR spectrum of **7** is 15.2 Hz, confirming the trans geometry of the newly generated double bond. The unsaturated ester was then reduced with DIBAL-H to yield alcohol **8** almost quantitatively, followed by iodination to afford allylic iodide **9** as fragment B.

The coupling of the fragment A with the fragment B via an S_N2 reaction[14] produced the alkene **10** in 50% yield. In the following step, Shapless asymmetric dihydroxylation (AD) reaction was utilized to install the chiral centers. When the AD reaction was carried out according to the standard procedure[12b] at rt, the ee value of the resulting diol was only about 55%. When the amount of chiral ligand, $DHQD_2PHAL$, was increased to 0.1 equiv, the ee value of the diol product **11** reached 87%, but the yield was just 31%. Finally, the HCl/MeOH catalytic system was employed to catalyze the deprotection and ring formation reactions simultaneously, affording the target structure **12** in yield of 58%. Meanwhile the *tert*-butyldimethylsilyl (TBS) protective group was removed as well for further structural extension.

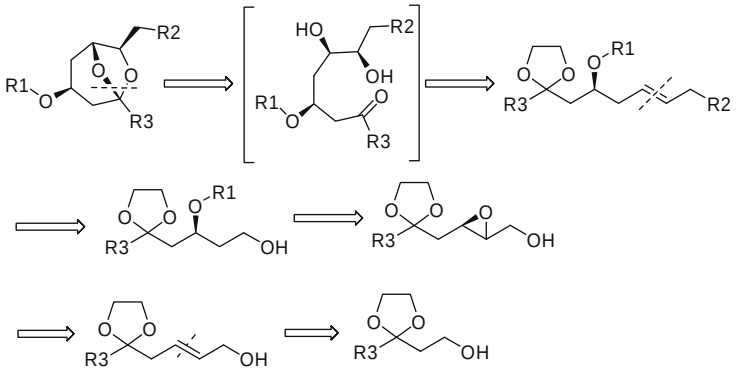


Scheme 2. Convergent stereoselective synthesis of the 3,5,7-trisubstituted-6,8-dioxabicyclo [3.2.1] octane.

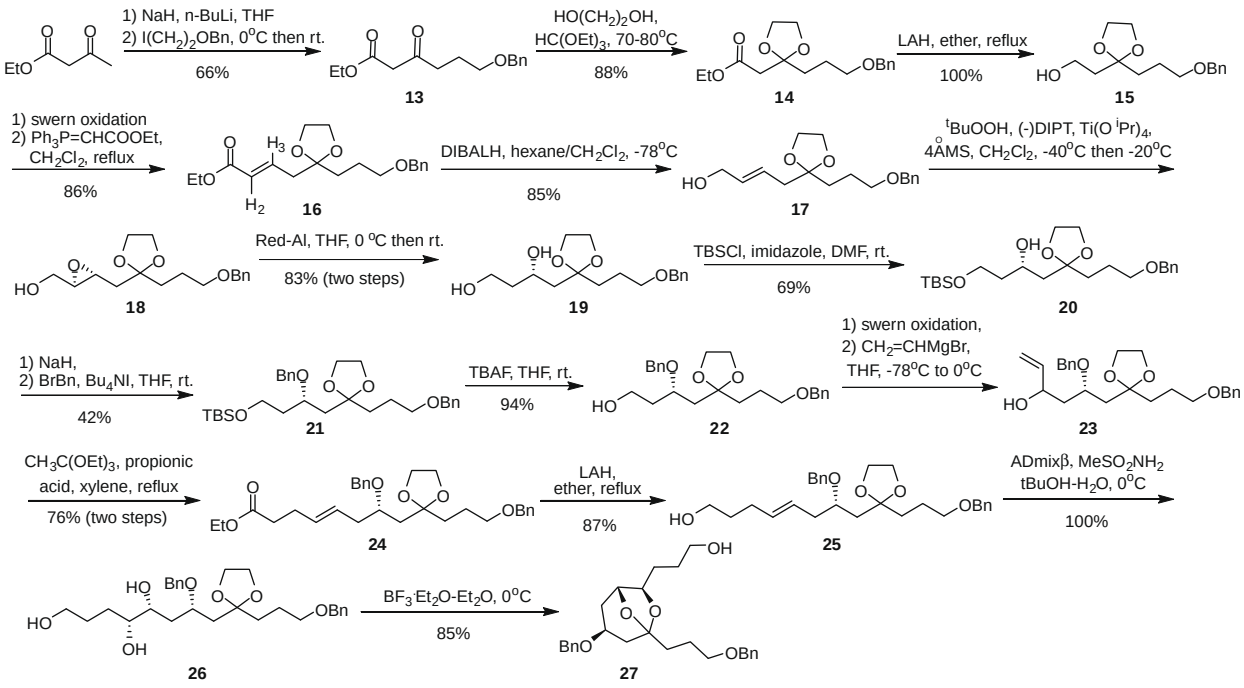
Strategy two: linear stereoselective synthesis

After successful synthesis of the core structure by convergent synthesis route, considering the flexible introduction of the chiral center at 3-position, we tried another linear synthesis route. According to the retrosynthetic analysis as shown in Scheme 3, the 3-position chiral center was installed before the ring-formation step, and kept intact through the whole retrosynthetic disconnection. Similar to strategy one, the bicyclic ketal structure was disconnected into a ketone and a diol group, then the diol group was further transformed into the alkene group. The alkene can be generated from 1,3-diol. The 1,3-diol moiety could be easily constructed by chemoselective ring opening of 2,3-epoxy alcohol with Red-Al.[15] And the 2,3-epoxy alcohol could be further transformed into the allylic alcohol, which could be easily prepared following the procedures described in strategy one. In this synthesis, the chiral centers could be introduced via Sharpless asymmetric dihydroxylation and Sharpless asymmetric epoxidation,[16] respectively.

As outlined in Scheme 4, the allylic alcohol **17** was conveniently synthesized by employing the approaches described in the former synthetic route. Sharpless asymmetric epoxidation (AE) reaction was utilized to synthesize the epoxy alcohol **18** in a stereoselective manner and introduced the 3-position chirality as desired. The ee value of the product is 87%. Chemoselective reduction of **18** with Red-Al afforded 1,3-diol **19**. After protection and deprotection procedures, hydroxyl group at the 3-position of **19** was finally protected as Bn ether, resulting in primary alcohol **22**. Probably owing to the stereohindrance, the reaction of 3-hydroxyl protection proceeded slowly and in low yield. Oxidation of compound **22** into aldehyde followed by treatment with vinyl Grignard reagent gave terminal alkene **23**. Following the Johnson–Claisen approach[17], compound **23** was transformed into (*E*)-alkene **24** via reaction with triethyl orthoacetate in xylene at refluxing temperature. Reduction of the ester **24** with lithiumaluminium hydride produced the alcohol **25**, then Sharpless AD reaction was again utilized to construct two chiral centers to afford triol **26**. The de value of the reaction cannot be calculated even with HPLC analysis,



Scheme 3. The retrosynthetic analysis of the 3,5,7-trisubstituted-6,8-dioxabicyclo [3.2.1] octane with strategy two.

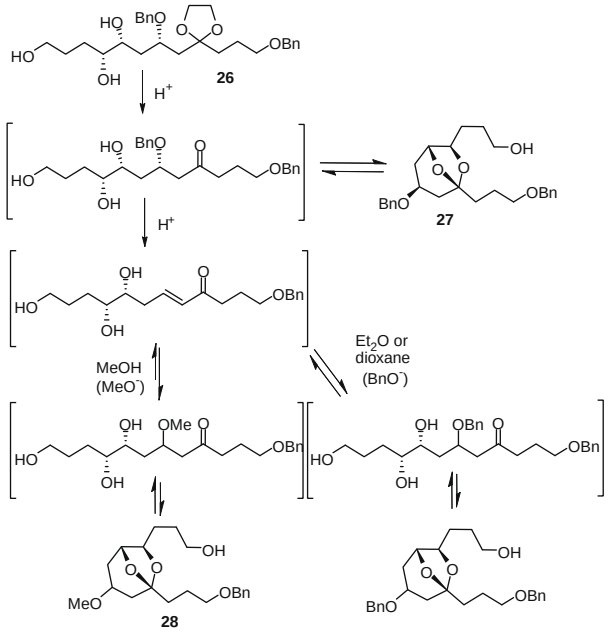


Scheme 4. Linear stereoselective synthesis of the 3,5,7-trisubstituted-6,8-dioxabicyclo [3.2.1] octane.

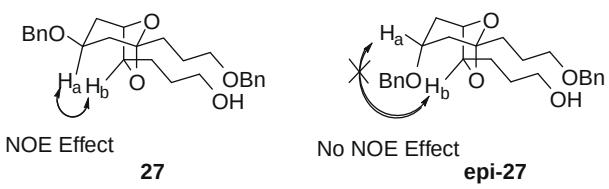
probably due to the similar polarity of compound **26** and its diastereoisomer, which just differed in the configuration at 1-and 7-position. However, the product was produced almost quantitatively in this reaction.

When HCl was used to catalyze the intramolecular ketal formation reaction in MeOH, which was a successful procedure in the former synthetic route, the exchange of benzyloxyl group to methoxyl group at 3-position was observed, leading to the side product **28**. When the solvent was changed to ether or dioxane, the epimerization at 3-position occurred. We proposed the mechanism of the side reaction as follows (Scheme 5): the reactant was easily eliminated to yield the α,β-unsaturated system with the catalysis of HCl. When MeOH was used as solvent, the methoxyl group attacked the unsaturated system via Michael-addition reaction. As a result, benzyloxy-methoxyl exchanged by-product generated. When ether or dioxane was used as solvent, there was no other nucleophile species present in the reaction system except for the benzyloxyl group, which was just eliminated from the reactant. So the benzyloxyl group attached again via 1,4-addition non-stereoselectively and caused epimerization. In order to prove the proposed mechanism, a drop of MeOH was added to the reaction system of catalytic amount of HCl in Et_2O, TLC revealed that there appeared benzyloxy-methoxyl exchanged by-product.

Since the proton acid HCl was the causing factor for the side reaction, we decided to try non-proton Lewis acid in the non-proton solvent such as Et_2O, to secure the desired dioxabicycle structure formation. As expected, the final step was successfully accomplished under the condition of $BF_3{\cdot}Et_2O$ in Et_2O at 0 °C, affording the alcohol **27** as the major product in yield of 85%. The configurations of **27** and its 3-epimer **epi-27** were determined with NOESY (Scheme 6). The existence of NOE effect between H_a and H_b revealed the *S* configuration of 3-position in compound **27**, while such NOE effect was not observed in the diastereoisomer **epi-27**.



Scheme 5. Proposed mechanism of side reaction in intramolecular ketal formation step.



Scheme 6. The NOE analysis of compound **27** and **epi-27**.

Considering the natural product cyclodidemniserinol trisulfate possessed both antitumor and HIV-1 integrase inhibitory activity, we chose tumor cell line (MDA-MB435) and HIV-1 integrase to evaluate the bioactivity of compound **27** and its 3-epimer **epi-27**. Neither compound showed inhibition against the HIV-1 integrase, indicating the important effect of the 22-memberd additional ring and the sulfate groups on the HIV-1 integrase inhibition. However, the compound **27** exhibited an IC_{50} value of 7.8 μM to inhibit the growth of the MDA-MB 435 cell, whereas the **epi-27** displayed no antiproliferative effect against the tumor cell line at the concentration of 20 μM, suggesting the importance of the 3-chirality on the antitumor activity. This interesting result provided useful clue for further structural elaboration and medicinal chemistry study of 3,5,7-trisubstituted 6,8-dioxabicyclo [3.2.1] octane-based focused library.

In conclusion, by employing either a convergent synthesis or a linear synthesis approach, we accomplished the construction of core structure 3,5,7-trisubstituted-6,8-dioxabicyclo [3.2.1] octane. In the context of further total synthesis, the two strategies were evaluated. In general, convergent synthesis strategy was made up of 13 reactions, with the longest route consisting of eight steps. The final trisubstituted bicycle structure was obtained in 0.9% overall yield with unsolved chirality at 3-position. However, the linear synthesis strategy encompassed 19 steps according to the longest route, with 5.3% overall yield and an unambiguous chirality at 3-postion.

Obviously, the lower yield of strategy one will hamper its application in total synthesis. Although the synthesis route was relatively long, strategy two was preferred for utilization in the total synthesis, because of its higher yield and the installed unambiguous chiral center at 3-postion. Furthermore, the preliminary biological assay provided interesting results of the 3,5,7-trisubstituted-6,8-dioxadicyclo [3.2.1] octane structure and its 3-eipmer in inhibiting the growth of the tumor cells. Our developed synthetic methodology will be beneficial for the further medicinal chemistry study and structural elaboration.

Acknowledgement

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Supplementary data

Synthetic procedure, NMR data and HRMS data of all new compounds; and ^1H and ^{13}CNMR spectra of important intermediates, including the gCOSY and NOESY spectrum of **27** and **epi-27**, are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.102.

References and notes

1. Mitchell, S. S.; Rhodes, D.; Bushman, F. D.; Faulkner, D. J. *Org. Lett.* **2000**, *2*, 1605–1607.
2. Gonzalez, N.; Rodriguez, J.; Jimenez, C. *J. Org. Chem.* **1999**, *64*, 5705–5707.
3. Haustedt, L. O.; Mang, C.; Siems, K.; Schiewe, H. *Curr. Opin. Drug Discov. Dev.* **2006**, *9*, 445–462.
4. Wood, D. L.; Browne, L. E.; Ewing, B.; Lindahl, K.; Bedard, W. D.; Tilden, P. E.; Mori, K.; Pitman, G. B.; Hughes, P. R. *Science* **1976**, *192*, 896–898.
5. Ellory, J. C.; Tucker, E. M. *Nature* **1969**, *222*, 477–478.

6. Pearce, G. T.; Silverstein, W. E. G. R. M.; Peacock, J. W.; Cuthbert, R. A.; Lanier, G. N.; Simeone, J. B. *J. Chem. Ecol.* **1975**, *1*, 115–124.
7. Araki, K.; Suenaga, K.; Sengoku, T.; Uemura, D. *Tetrahedron* **2002**, *58*, 1983–1995.
8. Uemura, D.; Chou, T.; Haino, T.; Nagatsu, A.; Fukuzawa, S.; Zheng, S.; Chen, H. *J. Am. Chem. Soc.* **1995**, *117*, 1155–1156.
9. Milroy, L. G.; Zinzalla, G.; Prencipe, G.; Michel, P.; Ley, S. V.; Gunaratnam, M.; Beltran, M.; Neidle, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 2493–2496.
10. Jun, J.-G. *Synlett* **2003**, *2003*, 1759–1777.
11. Masaki, Y.; Serizawa, Y.; Nagata, K.; Kaji, K. *Chem. Lett.* **1983**, *12*, 1601–1602.
12. (a) Ojima, I. *Catalytic asymmetric synthesis*; VCH: New York, NY, 1993; (b) Kobb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547. and references therein.
13. Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082–1087.
14. Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231–237.
15. Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719–2722.
16. Gao, Y.; Hanson, R. M.; Klundu, J. M.; Ko, S. Y.; Masamune, J.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
17. Nowicki, J. *Molecules* **2000**, *5*, 1033–1050.